amino acid, peptide or sugar residue, or alternatively, taken together, form a heterocycle,

Y represents $C(R_9)_2$, O, S, Nr', CHOH, CO, SO or SO_2,

Z_2 represents O, S or NR',

Z_3 represents O or S,

n, which may be identical or different, is equal to 0 or 1; p, which may be identical or different, is equal to 0, 1, 2 or 3; t is equal to 0, 1, 2 or 3; q is an integer between 0 and 10,

or a salt or isomer thereof.

55 (New). A method according to Claim 54, wherein said ophthalmological disorder is a corneopathy.--

REMARKS

Claims 28-30, 34-36 and 38-41, all of the claims previously in the application, have been cancelled, and new Claims 42-55 have been presented in their stead. The new claims have basis at least in original Claim 22 and on pages 1-7 and 18-20 of the specification as originally filed. For the Examiner's convenience, it is pointed out that new independent Claims 42, 51, 52, 53 and 54 replace previous independent Claims 28, 38, 39, 40 and 41, respectively. In new Claim 42, the dermatological condition is

defined as in previous Claim 29. In each of the independent claims, the language preceding the definition of the compounds has been clarified. In addition to new dependent claims paralleling the dependent claims previously in the application, there are new dependent claims which do not parallel previous dependent claims but which are fairly based on the original specification, pages 18-20. No new matter has been introduced.

At this time, applicants would like to address issues raised by the Examiner in the Advisory Action dated August 7, 2000.

With respect to the declaration discussed on page 2 of the Advisory Action, it is first noted that the fully executed declaration was submitted herein when applicants filed a Request for Continuing Prosecution Application on September 18, 2000. In the Advisory Action, the Examiner has pointed out that no copy of any publication describing the *in vitro* assay has been provided. This deficiency has been corrected by submitting herewith copies of the three descriptions of assays referred to on page 2 of the Demarchez declaration, namely the Bailey et al *Skin Pharmacology*, Levin et al *Nature* and Allenby et al *Proc. Natl. Acad. Sci. USA* publications. For the Examiner's convenience, these documents are listed on the accompanying Form PTO-1449.

The Examiner has also stated that even if it is true that some of the disclosed compounds will exhibit one or two activities in common with certain retinoids, it does not follow that the disclosed compounds will share all properties with retinoids or that

all retinoids are effective to treat any one form of cancer. However, it is obvious that all retinoids do not act in exactly the same way in the same pathology, since some are RAR agonists, some are RAR antagonists, some are RXR agonists and so forth. However, all retinoids interfere in cell proliferation/differentiation mechanisms and it is therefore reasonable to conclude that they are potentially effective in all pathologies related to these mechanisms.

The Examiner has also stated that no copy of a publication describing the ear edema assay has been provided, that the methodology is not clear, since it appears that the compound in question was first used to treat ear edema and subsequently treat it, and that there is no relationship between ear edema and cancer. In response, ear edema is not a pathology treated by retinoids and has no relation to cancer. Ear edema is a phenomenon induced by retinoids due to their specific activity and correlates with their clinical activity. Applicants enclose a copy of a poster presented at a meeting by Jomard et al describing ear mouse edema as a simple model for evaluating the *in vivo* activity of retinoic acid analogs; this is listed on the accompanying Form PTO-1449 for the Examiner's convenience. Moreover, these methods for evaluating the *in vivo* activity of retinoic acid analogs are described in United States Patents Nos. 5,696,104 and 5,827,500, copies of which are provided herewith and are also listed on the accompanying Form PTO-1449.

The Examiner has asked how acne, a dermatological condition, is related to cancer. As noted on page 769, Chapter 73 of *Fitzpatrick's Dermatology in General Medicine* (copy enclosed and listed on the accompanying Form PTO-1449), acne is a multifactorial disease. It develops in the sebaceous follicles and primarily alters the pattern of keratinization , that is, the proliferation and differentiation of keratinocytes, which occurs within the follicle in the canal of the infundibulum. In cancer, the cancerous cells are in a hyperproliferative state which leads to the growing of the number of malignant cells. It is further noted in Chapter 256, p. 2810, of the Fitzpatrick's text (copy enclosed and listed on Form PTO-1449), that retinoids have diverse biological effects. Thus, retinoids affect cell growth and differentiation; they also affect morphogenesis and inhibition of tumor promotion and malignant cell growth; further, they affect immunomodulatory actions as well as alterations in cell cohesiveness.

Consequently, it is generally thought that a reason why retinoids are useful in the treatment of acne is the normalization of the differentiative/proliferative states of the keratinocytes in the canal of the infundibulum. In the treatment of cancer, retinoids are also useful due to their antiproliferative, pro-differentiating effects on cancer cells. It is precisely this well-known influence on proliferation/differentiation on the cells in which the retinoids are expressed which makes retinoids efficient in the treatment of

both acne and cancer, even if these diseases at first thought seem to have nothing in common.

The Examiner has also queried whether antineoplastic compounds are generally effective in the treatment of, for example, psoriasis or eczema. In reply, because psoriasis represents excessive cellular proliferation and inflammation (cf. the aforenoted Fitzpatrick's text, Chapter 43, pp. 509-510, copy enclosed and listed on Form PTO-1449), it is apparent that compounds like retinoids can act in both the pathology of psoriasis and the pathology of cancer.

Moreover, there are in fact some compounds which are known to be effective in cancer and in psoriasis; see, for example, the above-mentioned Fitzpatrick's text, Chapter 255, pages 2798 and 2801 (copies enclosed and listed on Form PTO-1449), where it is noted first that methotrexate is one of the most commonly used antimetaboliles in cancer therapy (page 2798) and then that the largest, most widely accepted dermatological use of methotrexate in non-neoplastic disease is in the treatment of psoriasis.

Furthermore, Vitamin D receptor agonists have been shown to act on keratinocyte proliferation/differentiation (like RAR agonists), work in psoriasis (like RAR agonists) and also have been suggested for use in treating cancer (like RAR agonists). Abstracts of several articles related to this point are enclosed and listed on the accompanying Form PTO-1449.

As to use of the compounds in diabetes, several abstracts are enclosed and are listed on the accompanying Form PTO-1449 showing the use of RXR-specific retinoids is diabetes.

As to various other disorders mentioned in the instant application, further abstracts are enclosed and listed on the accompanying Form PTO-1449.

In view of the foregoing as well as the evidence already of record, it is submitted that the record 35 U.S.C. §112, first paragraph, rejection is untenable against the claims now in this application.

Favorable consideration on the merits is respectfully requested.

Respectfully submitted,

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Date: February 5, 2001